

BIOGRAPHICAL SKETCH

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NAME: **Paukert, Martin**

eRA COMMONS USER NAME (credential, e.g., agency login): mpauker1

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Eberhard Karls University of Tübingen, Germany		05/2001	Medicine
Eberhard Karls University of Tübingen, Germany	M.D.	11/2002	Physiology / Biophysics
Eberhard Karls University of Tübingen, Germany	Postdoctoral	06/2004	Physiology / Biophysics
Johns Hopkins University, Baltimore, Maryland	Postdoctoral	06/2010	Neuroscience

A. Personal Statement

My laboratory is interested in understanding neural processes that reflect awake behavior of mice. In this context we focus on the contribution of astroglia to neuromodulation. We apply cutting-edge microscopy technology and electrophysiology to investigate basic cellular and circuit mechanisms underlying arousal, shifts in attentional state and learning. Findings from our research are relevant for understanding neurodegenerative diseases such as Alzheimer's disease and neuropsychiatric diseases such as autism spectrum disorders, attention deficit hyperactivity disorder or post-traumatic stress disorder. We take comparative approaches to leverage the clear circuit architecture in the cerebellum and the high level of control over sensory stimulation in the primary visual cortex.

I received a formal training as medical doctor at the University of Tübingen in Germany and worked towards my MD thesis in the Department of Physiology with Drs. Ruppertsberg and Gründer on structure-function relationships of ATP and proton gated ion channels. I became interested in glial and cerebellar physiology when I joined Dr. Bergles' laboratory at the Johns Hopkins University School of Medicine for a postdoctoral fellowship. I focused on elucidating the role of the cerebellar molecular compartmentation for climbing fiber signaling. I found that climbing fibers release different amounts of glutamate depending on the zones within the cerebellar cortex they target, suggesting systematic differences in information processing dependent on the regions of the cerebellum. Recent technological advances make it more and more feasible to apply the rigor of cellular physiology to studies of intact circuits in behaving animals. With this goal, I built a two-photon microscope and equipped it for combining *in vivo* imaging with *in vivo* patch-clamp recording experiments. Furthermore, to enable the correlation of locomotion with Ca^{2+} signals in *GLAST-CreER;R26-lsl-GCaMP* mice, I developed a linear treadmill paradigm. I found that the neuromodulator norepinephrine plays a critical role in global activation of astroglia in the cerebellum as well as throughout the cerebral cortex during onset of locomotion. One of the major goals of my laboratory is to understand the meaning of this global activation of astroglia for neuronal activity and behavior. The analysis that I performed on electrophysiology, immunocytochemistry data and two-photon imaging required development of customized software routines in MATLAB. The Department of Physiology and the Center for Biomedical Neuroscience at University of Texas Health San Antonio provide a highly supportive environment, in which many investigators share an interest in synaptic and systems physiology.

Students in my laboratory will learn to evaluate the literature in order to conceptualize a research project, how to design experiments and controls to achieve unequivocal results and they will learn how to

publish their results. Computer programming skills are not required; however, students should not be shy of using and learning how to edit computer programs written in MATLAB. **The ideal students in my laboratory feel comfortable handling awake mice, learn to perform mouse surgeries and they consider physics and/or mathematics to be among their three favorite high school subjects.** Following the example of our current Xiangya medical student (Xiangyu Zhu, ZhuX5@uthscsa.edu), and our recent Xiangya medical student (Liang Ye, yenn1989@sina.cn), such skills combined with our generously equipped laboratory will enable the prospective student to conduct his/her own research project involving imaging of Ca²⁺ signals in nerve cells and glia in the brain through a cranial window while mice are awake.

B. Positions and Honors

Positions and Employment

2010-2013 Research Associate, Department of Neuroscience, Johns Hopkins University
 2013- Assistant Professor, Department of Physiology, University of Texas Health San Antonio
 2016- Core Faculty Member, UTSA/UTHSA Joint Biomedical Engineering Graduate Program

Professional Memberships

2003- Society for Neuroscience
 2010- American Chemical Society
 2014- The Optical Society

Research Services

2012-2015 Consultant ("in vivo imaging") to Professor Stanley A. Thayer, Department of Pharmacology, University of Minnesota, Minneapolis, MN
 2017- NIH - Early Career Review Program

Awards

1998-2000 Fellowship from the Graduiertenkolleg "Zellbiologie in der Medizin", Tübingen, Germany
 2001 FENS Fellowship for the FENS Summer School 2001, Ofir, Portugal
 2003 Plester Prize for the best medical thesis of the year at the University of Tübingen School of Medicine
 2005-2008 Postdoctoral Fellowship from the National Multiple Sclerosis Society

Invited Talks

09/2008 Department of Physiology, Rheinisch-Westfälische Technical University, Aachen, Germany
 06/2011 Center for Neurogenetics, University of Florida, Gainesville, FL
 04/2012 Department of Neuroscience, University of Minnesota, Minneapolis, MN
 01/2013 European Neuroscience Institute, University of Göttingen, Göttingen, Germany
 01/2013 Carl-Ludwig-Institute for Physiology, University of Leipzig, Leipzig, Germany
 03/2013 Department of Physiology, The University of Texas Health Science Center at San Antonio, San Antonio, TX
 04/2015 keynote speaker, Council for Excellence in Women's Health, The University of Texas Health Science Center at San Antonio, San Antonio, TX
 06/2015 The University of Texas Health Science Center at San Antonio, Planned Giving Advisory Council meeting
 09/2015 Department of Biology, Trinity University, San Antonio, Texas
 11/2015 Department of Physiology, Seoul National University, Seoul, South Korea
 11/2015 2015 SKKU Symposium on Molecular Medicine, Sungkyunkwan University School of Medicine, Seoul, South Korea
 07/2016 Cold Spring Harbor Laboratory Meeting, Glia in Health & Disease
 09/2016 Department of Neurobiology, University of New Mexico, Albuquerque
 09/2016 Department of Biology, Neurobiology Seminar, UTSA
 10/2016 Texas FreshAIR Initiative, Austin
 02 / 2017 Winter Conference on Brain Research, Big Sky, Montana

04 / 2017 Department of Molecular, Cellular and Biomedical Sciences, University of New Hampshire, Durham

04 / 2017 South Texas Center for Emerging Infectious Diseases, UTSA

C. Contribution to Science

1. Alcohol consumption has acute effects on motor coordination as well as on our ability to pay attention. Norepinephrine is playing a central role in attention and it has been known since the early 1980s that ethanol can inhibit the excitability of locus coeruleus neurons. Locus coeruleus neurons synthesize norepinephrine and release it from their terminals throughout the brain. While this finding suggested that ethanol could inhibit norepinephrine release, it has been difficult to assess the consequences of ethanol exposure for adrenergic receptor activation on target cells. In previous in vivo two-photon Ca^{2+} imaging studies (contribution 3.) we found that locomotion induces a widespread global Ca^{2+} activation of Bergmann glia and cortical astrocytes in a norepinephrine-dependent manner. Furthermore, we found that noradrenergic activation of astrocytes was necessary for these cells to encode sensory input in global Ca^{2+} signals. Here, in my independent lab, we found that ethanol can dose-dependently inhibit behavioral state-dependent global astroglia Ca^{2+} elevations. In contrast, microdomain Ca^{2+} dynamics in cortical astrocytes were facilitated by ethanol. This study revealed a potentially central role of astroglia in mediating acute effects of alcohol exposure.

Ye[#], L., Orynbayev[#], M., Salinas, A., Zhu, X., Paukert*, M. (in preparation). Impairment of astroglia Ca^{2+} activation by ethanol and consequences for local circuit activity. * corresponding author, [#] co-first author

2. The development of genetically encoded Ca^{2+} sensors has been progressing rapidly in recent years. We and others in the field are transitioning from using GCaMP3 to newer versions of GCaMPs. This situation raises the question how data obtained with different sensor variants in different laboratories can be related to each other. To provide guidance in this regard my laboratory has recently completed a systematic comparison of GCaMP3 and GCaMP6f signals of astrocyte Ca^{2+} dynamics in awake behaving mice covering all scales: global, waves along processes and microdomain. We found that GCaMP6f is noticeably more sensitive for the detection of microdomain Ca^{2+} events as well as Ca^{2+} waves along individual astrocyte processes. In contrast, we found only minor differences in the kinetics of astrocyte global Ca^{2+} responses.

Ye, L., Haroon, M.A., Salinas, A., Paukert*, M. (revision submitted). Comparison of GCaMP3 and GCaMP6f for in vivo monitoring of astroglia Ca^{2+} dynamics. * corresponding author

3. Research during the recent decade has revealed that neural signaling on the cellular level is strongly dependent on the behavioral activity state of an animal. Most progress in this new field has been made using experimental paradigms, which allow to monitor whether a mouse is resting or walking on a treadmill. For example, it has been found that locomotion can increase the gain with which primary visual cortex pyramidal neurons process visual information and it can lead to a temporary, global Ca^{2+} elevation in astroglia. To understand behavior-induced astroglia activation more mechanistically I used transgenic mice, which express the genetically encoded Ca^{2+} sensor GCaMP3 selectively in astroglia allowing for an unambiguous interpretation of Ca^{2+} imaging data. Furthermore, I developed a motorized linear treadmill paradigm. The motorization has two major advantages – motor-induced astroglia activation is much more robust, which facilitates quantification of pharmacological experiments, and it gives the experimenter control over the timing of locomotion, which facilitates the coordination with other sensory stimuli. Taking advantage of these benefits I discovered that noradrenergic signaling is not only necessary for locomotion-induced activation of astroglia in motor-related regions such as the cerebellum, it even leads to coordinated activation of astroglia throughout the CNS. Moreover, noradrenergic signaling seems to be required for astroglia to participate in processing of sensory information. These findings raise fundamental questions on the sequence of events leading to activation of astroglia as well as neurons during locomotion and on consequences of astroglia activation for neuronal signaling. The current proposal aims to address these questions.

- a. Paukert^{**}, M., Agarwal[#], A., Cha, J., Doze, V.A., Kang, J.U. and Bergles*, D.E. (2014). Norepinephrine controls astroglial responsiveness to local circuit activity, Neuron **82(6)**, 1263-1270. * corresponding author, # co-first author
 - b. Cha*, J., Paukert, M., Bergles, D.E. and Kang, J.U. Fiber-optic fluorescence microscopy for functional brain imaging in awake, mobile mice. SPIE Photonics West BO 8928-92, San Francisco, Feb 1, 2014. * oral presentation & peer-reviewed conference publication
 - c. Paukert*, M. and Bergles, D.E. (2012). Reduction of motion artifacts during *in vivo* two-photon imaging of brain through heartbeat triggered scanning. Journal of Physiology **590(Pt 13)**, 2955-2963. * corresponding author
4. In previous work I studied the functional organization of the cerebellar circuitry. The cytoarchitectural layout of the cerebellum is simple when compared to cortical circuits and appears uniform throughout the cerebellum. However, when the expression pattern of individual molecules such as the glycolytic enzyme aldolase C (zebrin II) is investigated, a modular band expression pattern becomes apparent. I used transgenic mice to identify Purkinje neurons, the principal neurons of the cerebellar cortex, from different aldolase C bands. I discovered systematic differences in the amount of glutamate released from climbing fiber terminals depending on which band the targeted Purkinje cell belonged to. This body of work revealed insight into the macroscopic organization of synaptic signaling in the cerebellum.
- Paukert, M., Huang, Y.H., Tanaka, K., Rothstein, J.D. and Bergles, D.E. (2010). Zones of enhanced glutamate release from climbing fibers in the mammalian cerebellum. Journal of Neuroscience **30**, 7290-7299.
5. My early work focused on understanding which structural elements determine the sensitivity of Acid Sensing Ion Channels (ASICs) for protons and how this sensitivity is affected by extracellular Ca²⁺ ions. ASICs are potential targets for novel pain medication and understanding structure-function relationships is a prerequisite for designing rational drugs.
- a. Paukert*, M., Chen, X., Polleichtner, G., Schindelin, H. and Gründer*, S. (2008). Candidate amino acids involved in H⁺ gating of acid-sensing ion channel 1a. Journal of Biological Chemistry **283**, 572-581. *corresponding author
 - b. Paukert, M., Babini, E., Pusch, M. and Gründer, S. (2004). Identification of the Ca²⁺ blocking site of acid-sensing ion channel (ASIC) 1: implications for channel gating. Journal of General Physiology **124**, 383-394. [PMCID: PMC2233906]
 - c. Babini*, E., Paukert*, M., Geisler, H.-S. and Gründer, S. (2002). Alternative splicing and interaction with di- and polyvalent cations control the dynamic range of acid-sensing ion channel 1 (ASIC1). Journal of Biological Chemistry **277**, 41597-41603. * co-first author

Full list of published work:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/martin.paukert.1/bibliography/48331674/public/?sort=date&direction=ascending>

D. Research Support

Active

Kleberg Foundation

Paukert (PI)

01/01/2015 – 12/31/2019

Mechanisms of neurodegeneration and the role of astrocytes: insights into Alzheimer's disease and its progression

This grant focuses on astrocytes and allows us to investigate the genetic reversibility of astrocyte dysfunction associated with Alzheimer's disease. Furthermore, it supports to study the role of specific adrenergic receptors in astrocytes in the context of disease progression.

Role: PI

CBN 2017 PILOT PROJECT-Lee

Lee (PI)

02/01/2017 - 01/31/2018

Cellular and Functional Role of Microglia in Fragile X Syndrome

This grant focuses on investigating morphological and functional alterations in microglia in a mouse model of Fragile X Syndrome.

Role: Co-I

UTS BRAIN #364828

Paukert (PI)

09/01/2015 - 08/31/2017

Brain circuit function and locus coeruleus

This grant focuses on establishing strategies to investigate brain state-dependent Ca^{2+} dynamics simultaneously in astrocytes and neurons.

Role: PI

Pending

1 R01 MH113780-01

Paukert (PI)

09/01/2017 - 08/31/2022

The Role of Astroglia in Brain State-Dependent Neural Activity

This grant focuses on understanding molecular mechanisms underlying the control of the functional interplay between cerebellar Bergmann glia and Purkinje cells during transitions in awake behavioral state by long-range noradrenergic signaling.

Role: PI (CMBG - 02/2017: 7%)

Completed

CBN 2015 PILOT PROJECT-Paukert

Paukert (PI)

01/01/2015 – 12/31/2015

Electrochemical tracking of behavioral state-dependent norepinephrine release

This pilot grant supported the establishment of electrochemical measurements in awake behaving mice.

Role: PI

1R03AA022239-01

Paukert (PI)

07/01/2013 - 06/30/2015

Effect of ethanol on Bergmann glia Ca^{2+} dynamics during motor behavior

This grant used two-photon imaging of transgenic mice expressing the genetically encoded Ca^{2+} sensor GCaMP3 in astroglia (GLAST-CreER;R26-lsl-GCaMP3) in combination with a treadmill motor behavior paradigm. The aim was to understand the effect of acute and chronic ethanol exposure of adult mice on locomotion-induced Ca^{2+} elevations in cerebellar Bergmann glia.

Role: PI

5P30AG013319-20/Paukert

Paukert (PI)

07/01/2014 – 06/30/2015

Behavior-induced astrocyte Ca^{2+} dynamics in aging/neurodegeneration

Nathan Shock Aging Center

This pilot grant allowed us to establish the APP;PS1;GLAST-CreER;R26-GCaMP3 mouse line to study astrocyte Ca^{2+} dynamics during accelerated aging.

Role: PI

Dear Xiangya student,

My laboratory is interested in understanding the role of the interaction between astrocytes and neurons in the brain and its importance for adjustments in neural activity associated with awake brain states. Our brain processes information differently whether we are paying close attention, or whether we are inattentive. The experimental approach that we are employing in our lab to study brain state-dependent signaling involves transgenic mice that express Ca^{2+} sensors in specific cell types and we use two-photon microscopy to visualize Ca^{2+} dynamics while the mice are either sitting at rest, or walk on a linear treadmill. We conduct mouse brain surgeries to prepare the animals for experiments and we use MATLAB software routines for data analysis. Other techniques comprise electrophysiology, molecular biology and immunofluorescence analysis of fixed brain tissue. Our studies are relevant to understand alterations in brain function during neuropsychiatric or neurodegenerative diseases.

Like with my recent Xiangya student Liang Ye (yenn1989@sina.cn) and my current student Xiangyu Zhu (ZhuX5@uthscsa.edu), with future Xiangya medical students I intend to maintain the aim to let them work on projects that despite their technical complexity allow a smart, motivated student without prior lab experience to either complete the project within two years, or at least contribute the lion's share. In concrete terms, for the prospective student I anticipate a study, which will use new red fluorescent genetically-encoded Ca^{2+} sensors that we have recently established in the lab. The student will combine these sensors with well established green sensors for two color simultaneous Ca^{2+} imaging in astroglia and neurons in the brain of awake behaving mice. By analyzing spatial distribution and timing of Ca^{2+} dynamics, the aim will be to build a hierarchical model of astroglia-neuron interaction in the intact brain and investigate the underlying mechanisms using pharmacological and genetic manipulations. We will also include electrophysiological experiments with the aim to relate Ca^{2+} signals to the electrical activity of neurons.

The prospective student will benefit from a uniquely equipped lab and peer students with hands-on experience on all aspects of the projects, including mouse brain surgeries, in vivo two-photon Ca^{2+} imaging of head-fixed awake mice and data analysis using custom-written software routines in MATLAB. I will be personally available for help with all aspects of the experimentation as well as for discussions of the scientific concept. The student will actively participate in weekly lab meetings and learn how to relate his/her work to the literature and effectively communicate research results in oral and written form.

Since almost all experiments in my lab involve operation of fairly complicated electrical or optical equipment, a firm intuitive approach to physical principles and a solid handling of numbers is critical for the success of all trainees in my lab.

Kind regards,
Martin Paukert